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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: September 11, 2014

SUBJECT: **Boscalid.** Human Health Assessment Scoping Document in Support of Registration Review.

PC Code: 128008
Decision No.: 488835
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D418673
Registration No.: NA
Regulatory Action: Registration Review
Case No.: 7034
CAS No.: 188425-85-6
40 CFR: §180.589

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Executive Summary

Attached is the Health Effects Division's (HED's) human health risk assessment scoping document for the fungicide boscalid to support Registration Review. To evaluate the scope of work necessary to support Registration Review, HED has considered recent risk assessments for boscalid, updates to its toxicity, exposure and usage databases, and the latest Agency science policy and risk assessment methodologies. The most recent risk assessment for boscalid was conducted in 2013 for numerous new uses (D405063, B. O'Keefe, 08/22/2013).

9/23/14

Boscalid is currently registered for use on numerous agricultural crops, as a seed treatment, on golf course turf, residential ornamentals, landscape gardens, residential fruit and nut trees, and greenhouse grown tomato transplants for the home consumer market. The HED review of the proposed new uses of boscalid on herb subgroup 19A and dill seed is pending (EPA Notice of Filing: EPA-HQ-OPP-2013-0798).

The toxicology database for boscalid is adequate for risk assessment. However, a subchronic inhalation study is required because the use of an oral point of departure (POD) results in margins of exposure (MOEs) as low as 370 for occupational exposure, which does not meet the target MOE for a waiver (MOE = 1000). The HED Hazard and Science Policy Council (HASPOC) has determined that this inhalation study will provide a more accurate evaluation of inhalation risk to boscalid (HASPOC, TXR0056585, K. Rury, 03/07/2013). Therefore, in the absence of a subchronic inhalation toxicity study a 10x database uncertainty factor has been added for inhalation exposure.

In repeated dose studies, the primary target organs are the liver and the thyroid (indirectly from liver adaptive response). Body weight decreases also have been observed in rats, mice and dogs. There are no concerns for neurotoxicity, immunotoxicity, or mutagenicity. The Cancer Assessment Review Committee (CARC) classified boscalid as "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", and, therefore, the quantification of human cancer risk is not recommended (TXR0051289, J. Kidwell, 11/14/2002).

Based on the available data, toxicity endpoints and PODs have been selected for chronic dietary, short-term incidental oral, and short- and intermediate-term dermal and inhalation exposure scenarios. Since no observed effects could be attributed to a single dose, an acute endpoint for acute dietary exposure was not established. Dermal absorption is 15%. The Food Quality Protection Act (FQPA) Safety Factor can be reduced to 1X because there is low concern for increased susceptibility and no residual uncertainties for pre- and post-natal toxicity in the available developmental, reproductive, and neurotoxicity studies used for risk assessment, and there are no residual uncertainties in the exposure database.

The residue chemistry database is sufficient to support current registrations of boscalid. The nature of the residue in plants and livestock has been adequately defined. Adequate field trial, rotational crop, livestock feeding, analytical method, primary crop processing, and storage stability data are available.

New dietary exposure and aggregate risk assessments are not anticipated during Registration Review, unless there are significant increases to the drinking water exposure estimates that need to be incorporated.

New occupational and residential handler and post-application exposure and risk assessments are not anticipated to be needed during Registration Review. However, if results from the recommended to be required subchronic inhalation study change the endpoints and result in lower PODs for occupational and residential handler exposures, then new occupational and

residential handler exposure and risk assessments, and new aggregate risk assessments may be needed.

The Agency will examine the need for spray drift and volatilization assessments during Registration Review for boscalid based on the potential for exposure to bystanders from agricultural applications.

Introduction

Boscalid, 3-pyridinecarboxamide, 2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl), is a fungicide active ingredient that works inside the mitochondria of fungi and stops fungi from producing the energy that they need to carry on basic functions. Boscalid prevents energy production by binding to the enzyme succinate ubiquinone reductase.

The most recent human health risk assessment for boscalid was finalized in 2013 for numerous new uses (D405063, B. O'Keefe, 08/22/2013). A new use risk assessment is pending for boscalid use on herb subgroup 19A and dill seed as well as crop group conversions on stone fruit group 12-12 and tree nut group 14-12. Boscalid is currently registered for use on numerous agricultural and orchard crops, and as a seed treatment. It is also registered for use on golf course turf, gardens, residential fruit and nut trees, ornamentals, including shrubs and bushes, and on tomato plants meant to be transplanted into home gardens. Homeowners may apply boscalid to residential gardens, as well as fruit and nut trees. Boscalid end use products are formulated as the following formulation types: emulsifiable concentrates, flowable concentrates, soluble concentrates, soluble concentrate/solid, water dispersible granules, and ready-to-use solutions. Boscalid is also formulated into products with other fungicides or insecticides. Applications can be made with ground, aerial, airblast, chemigation, hand held, or seed treatment equipment. Refer to Attachment 1 (Table 1) for the chemical identity of boscalid.

Hazard Identification/Toxicology

The toxicology database for boscalid is adequate for risk assessment, except for a subchronic inhalation study. All other toxicity data requirements for conventional pesticide registration under the current 40 CFR §158.500 have been satisfied. All studies needed to assess susceptibility concerns, such as developmental and reproduction studies, have been submitted. Additional studies, such a developmental neurotoxicity study, acute and subchronic neurotoxicity studies and an immunotoxicity study are also available. The subchronic inhalation study is recommended to be required because the use of an oral POD results in MOEs as low as 370 for occupational exposure, which does not meet the target MOE for a waiver (MOE = 1000) (HASPOC, TXR0056585, K. Rury, 03/07/2013). Therefore, in the absence of a subchronic inhalation toxicity study a 10x database uncertainty factor has been added for inhalation exposure.

In mammals, the primary target organs are the liver and the thyroid (indirectly from liver adaptive response). In subchronic and chronic feeding studies in rats, mice and dogs, boscalid generally caused decreased body weights and body weight gains (primarily in mice) and effects on the liver (increase in weights, changes in enzyme levels and histopathological changes) as

uncertainty. For example, when assessing residential post-application exposure to gardens and ornamentals, EPA assumes the following: exposures occur to zero-day (i.e., day of application) residues every day of the assessed exposure duration (i.e., EPA assumes that no dissipation or degradation occurs, it doesn't rain, etc); individuals perform the same post-application activities performed in the transfer coefficient study day after day (e.g., weeding, harvesting, pruning, etc.); and individuals engage in these post-application activities for a high-end amount of time every day (represented by data reflecting time spent gardening based on survey data).

Given the conservatisms discussed above and the potential compounding nature of these conservatisms, EPA is able to rely upon the calculated exposure estimates with confidence that exposure is not being underestimated. Since the estimated residential post-application exposure for residential gardens using default DFR values for boscalid is minimal in comparison to the level of concern (i.e., the calculated MOE is greater than 2 times higher than the level of concern, MOE = 690 compared to the LOC of 100); EPA is waiving the 40 CFR §158 DFR data requirement. In this instance, it is unlikely that chemical-specific DFR data would be needed to further refine exposure assessments or would add appreciably to our overall understanding of the availability of dislodgeable foliar pesticide residues for boscalid.

Spray Drift or Volatilization

Residential exposures resulting from off-site transport (e.g., spray drift or volatilization) may occur as a result of boscalid applications to agricultural fields. Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for boscalid. The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information).[1] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides.

Residential bystander exposures resulting from off-site transport (e.g., spray drift or volatilization) may occur as a result of applications of boscalid. The potential for spray drift will be evaluated for each pesticide during the Registration Review process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) Standard Operating Procedures for Residential Risk Assessment (SOPs) – Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift. This document outlines the quantification of indirect non-occupational exposure to drift. In terms of volatilization, the agency has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for boscalid.

Conclusions: The need for new residential handler and post-application exposure and risk

[1] Available: http://www.epa.gov/opp00001/factsheets/spraydrift.htm

assessments are not anticipated during Registration Review. However, if results from the recommended to be required subchronic inhalation study change the endpoints and result in lower PODs for residential handler exposures, then new residential handler exposure and risk assessments may be needed. Additionally, during Registration Review the Agency will examine the need for a volatilization assessment, as well as the potential for exposure from spray drift, to assess post-application residential risk from boscalid during Registration Review.

A chemical specific TTR study is not recommended to be required at this time for boscalid since the lowest dermal MOE (10,000) is greater than 10 times the LOC based on default values for the fraction of application rate available for transfer after a turf application. Additionally, DFR studies are not recommended to be required at this time for boscalid since the lowest dermal MOE (690) is greater than two times the LOC based on default input values.

Aggregate Risk Assessment

Aggregate assessments consider exposures from food, drinking water, and residential uses. Since there are residential uses of boscalid, aggregate risk considers residential handler and post-application exposures, food, and drinking water.

In the most recent human health risk assessment (D405063, B. O'Keefe, 08/22/2013), an acute aggregate risk assessment, which is equivalent to the acute dietary risk assessment, was not conducted, since no observed effects could be attributed to a single dose, and therefore, an acute endpoint was not established.

A short-term aggregate risk assessment, which included dermal exposures combined with background chronic dietary (food and drinking water) exposures, resulted in MOEs ranging from 290 to 690 (LOC = 100). The greatest adult non-cancer aggregate exposure risk estimate is not of concern to HED; the MOE is 290, which is greater than the LOC of 100. The aggregate MOEs for youths (11-16 years old) and children (6-11 years old) were 690 and 310, respectively.

Chronic exposure from the residential pathway is not anticipated based on the current boscalid use pattern. Therefore, the chronic aggregate risk (food and drinking water) is equivalent to the chronic dietary (food and drinking water) exposure estimate.

Conclusions: Aggregate exposure to boscalid is currently not of concern to HED. New aggregate assessments are not anticipated to be needed during Registration Review, unless changes in uses, procedures, or EDWCs occur, or if results from the recommended to be required subchronic inhalation study change the endpoints and PODs for residential handler exposures.

Occupational Exposure

Boscalid is registered for use on numerous agricultural use sites. It is also registered for occupational use on several non-agricultural use sites. There is potential for short- and intermediate-term occupational exposure to boscalid during handling (mixing, loading, and applying) and post-application activities.

Occupational Handlers

Previous occupational handler exposure and risk assessments for boscalid were conducted at the maximum application rate and assumed the maximum area treated per day for all the registered agricultural use sites. The registered boscalid labels require occupational handlers to wear long-sleeved shirts, long pants, shoes, socks, and chemical resistant gloves. Applications can be made with ground, aerial, airblast, chemigation, hand held, or seed treatment equipment. All current exposure estimates at baseline personal protective equipment (PPE) (single layer clothing, no gloves, and no respirator) were not of concern (ARIs >1). Using current HED standard operating procedures (SOPs), all handler risk estimate ARIs ranged from 1.1 to 95. Therefore, an updated occupational handler risk assessment is not needed during Registration Review, unless results from the recommended to be required subchronic inhalation study change the endpoints and PODs for occupational handler exposures.

Occupational Post-Application

Occupational post-application short- and intermediate-term dermal exposures are possible for workers tending treated food crops. All post-application scenarios for all crops resulted in dermal MOEs greater than 100 on day 0 (12 hours after application), and therefore, are not of concern to HED. Using current HED SOPs, risk estimate MOEs for dermal exposure ranged from 400 to 21,000. Labels of registered boscalid products require restricted entry intervals (REIs) of 12 hours, which is adequate to protect agricultural workers from post-application exposures to boscalid.

Turf Transferrable Residue (TTR) Data

In accordance with 40 CFR §158, TTR data are required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses that could result in post-application exposure to turf. In the absence of chemical-specific TTR data, EPA uses default values. As detailed in the Residential Post-Application section of this document, the estimated occupational turf post-application exposure for workers using default TTR values for boscalid is minimal in comparison to the level of concern (i.e., the calculated MOE is greater than 10 times higher than the level of concern, lowest dermal MOE = 10,000 compared to the LOC of 100); HED is recommends waiving the 40 CFR §158 TTR data requirement. In this instance, it is unlikely that chemical-specific TTR data would be needed to further refine exposure assessments or would add appreciably to our general understanding of the availability of turf transferable pesticide residues for boscalid.

Dislodgeable Foliar Residue (DFR) Data

In accordance with 40 CFR §158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. In the absence of chemical-specific DFR data, EPA uses default values. As detailed in the Residential Post-Application section of this document, the highest estimated occupational post-application exposure for agricultural crops using default DFR values for boscalid is minimal in comparison to the level of concern (i.e., the calculated MOE is greater than 2 times higher than the level of concern, MOE = 400 compared to the LOC of 100); and therefore, HED recommends waiving the 40 CFR §158 DFR data requirement. In this instance, it is unlikely that chemical-specific

DFR data would be needed to further refine exposure assessments or would add appreciably to our overall understanding of the availability of dislodgeable foliar pesticide residues for boscalid.

Conclusions: There is sufficient information available to assess occupational handler and post-application exposures. Updated occupational handler and post-application exposure assessments are not anticipated to be needed during Registration Review. However, if results from the recommended to be required subchronic inhalation study change the endpoints and result in lower PODs for occupational exposures, then new occupational handler exposure and risk assessments may be needed. Chemical-specific DFR data were not previously submitted. However, DFR studies are not recommended to be required at this time for boscalid since the lowest dermal MOE of 400 is greater than two times the LOC based on default input values. Also, a chemical specific TTR study is not recommended to be required at this time for boscalid since the lowest dermal MOE (10,000) is greater than 10 times the LOC based on default values for the fraction of application rate available for transfer after a turf application.

Public Health and Pesticide Epidemiology Data

Based on the low frequency and severity of incident cases reported for boscalid in both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR), there does not appear to be a concern at this time that would warrant further investigation. For the Main IDS, from January 1, 2009 to May 28, 2014, there was 1 incident reported for the single chemical only in the database. There were 2 additional incidents reported involving more than one chemical. These incidents were classified as moderate severity. In Aggregate IDS, from January 1, 2009 to May 28, 2014, there were 6 incidents reported involving boscalid. These incidents were classified as minor severity. Overall, there are few incidents involving boscalid reported to IDS.

A query of the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides database for 1998-2010 identifies 10 cases involving boscalid. All cases involved multiple active ingredients. All 10 cases were work-related; seven cases involved field workers and three cases involved applicator/handler exposures. Nine cases occurred in Washington and at least five cases involved orchard fruit production. Eight cases were low in severity and two cases were moderate in severity. Dermal symptoms were most frequently reported.

The Agricultural Health Study (AHS) is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. The AHS includes private and commercial pesticide applicators and their spouses. If there are AHS findings relevant to a particular pesticide going through registration review, the Agency will ensure they are considered in the problem formulation/scoping phase of the process and, if appropriate, fully reviewed in the risk assessment phase of the process. The AHS includes information on use of 50 different pesticide active ingredients commonly used in agriculture. Boscalid is not included in the AHS, and therefore, this study does not provide information for this report.

The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Conclusion: Based on the low frequency and low severity of incident cases reported for boscalid in both IDS and SENSOR-Pesticides databases, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Tolerance Assessment and International Harmonization

Permanent tolerances have been established under 40 CFR §180.589(a)(1) for residues of boscalid (with compliance determined by measuring only boscalid) in plant commodities, ranging from 0.05 ppm in/on green coffee beans, peanuts and tuberous and corm vegetables (subgroup 1C) to 85.0 ppm in citrus oil. Separate tolerances have also been established for indirect or inadvertent residues of boscalid (with compliance determined by measuring only boscalid) in rotational crops under 40 CFR §180.589(d) at levels ranging from 0.05 to 8.0 ppm. Tolerances for livestock commodities have been established under 40 CFR §180.589 (a)(2) for residues of boscalid (with compliance determined by measuring the combined residues of boscalid and its metabolites 2-chloro-*N*-(4′-chloro-5-hydroxy-biphenyl-2-yl)nicotinamide and the glucuronic acid conjugate of the 5-hydroxy metabolite) at levels ranging from 0.02 ppm in eggs to 0.35 ppm in meat byproducts of cattle, goats, horses, and sheep.

The US, Codex, and Canadian residue definitions for tolerance for plant commodities are harmonized with a definition of boscalid. The US and Canada residue definitions for livestock commodities are harmonized, but not harmonized with Codex.

Generally, US and Canadian tolerances/MRLs are harmonized for some plant commodities and the majority of livestock commodities. The tolerances/MRLs are harmonized for canola oil, cucumber, pome fruit, cereal grains, raisin, dried hops, leaf petioles subgroup 4B, leaf greens subgroup 4A, head lettuce, dried shelled peas and beans subgroup 6C, tree nut group 14, succulent shelled peas and beans subgroup 6B, peanut, peanut oil, peppermint, pistachio, soybean, spearmint, edible podded legume vegetables subgroup 6A, tuberous and corm vegetables subgroup 1C, cattle and goat and horse and sheep fat, cattle and goat and horse and sheet and poultry meat, cattle and goat and horse and sheep meat byproducts, egg, and milk. US tolerances are greater than Canadian MRLs for bushbery subgroup 13-07B, caneberry subgroup 13-07A, Belgium endive, small fruit vine climbing subgroup 13-07F, stone fruit group 12, oilseed group 20, soybean vegetable, turnip greens, bulb vegetable group 3-07, cucurbit vegetable group 9, fruiting vegetable group 8-10, root vegetable subgroup 1A, poultry fat, and poultry meat byproducts. US tolerances are less than the Canada MRLs for Brassica head and stem vegetables subgroup 5A, Brassica leafy greens vegetables subgroup 5B, leaf lettuce, hog fat, hog meat, and hog meat byproducts. The latter may be amenable to harmonization via increasing US tolerances.

Most Codex and US tolerances are not harmonized. Codex and US tolerances are the same for caneberry subgroup 13-07A, coffee, citrus fruit, pome fruit (apple only), small fruit vine

climbing 13-07F (grape only), bulb vegetable group 3-07, and fruiting vegetable group 8-10. Some US tolerances are lower than Codex MRLs and might be increased for purposes of harmonization. However, such changes would disharmonize with Canada for cereal grains, raisin, dried hops, dried shelled peas and beans subgroup 6C, succulent shelled pea and bean subgroup 6B, and pistachio. Tolerance harmonization issues will be evaluated during registration review.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, will be considered in the registration review, in accordance with US Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled under the NHANES/WWEIA and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Cumulative

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to boscalid and any other substances and boscalid does not appear to produce a toxic metabolite produced by other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Human Studies

The risk assessments which have been previously conducted for boscalid relied in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many

different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED), the Outdoor Residential Exposure Task Force (ORETF), and the Agricultural Reentry Task Force (ARTF) Database. EPA has reviewed all the studies supporting these multi-pesticide generic exposure databases, and has found no clear and convincing evidence that the conduct of any of them was either fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. All applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied, and there is no regulatory barrier to continued reliance on these studies.

Data Deficiencies

870.3465 Subchronic Inhalation study

- A subchronic inhalation study is recommended to be required because the use of an oral point of departure for inhalation exposure results in MOEs as low as 370 for occupational exposure, which is not sufficient to alleviate concern (HASPOC, TXR0056585. K. Rury. 03/07/2013). Therefore, a 10X database uncertainty factor has been added for inhalation exposures.

No additional residue chemistry, or occupational and residential exposure data are needed to support the registered uses of boscalid at this time.

References

Recent Memoranda Relevant to Registration Review of Boscalid			
Author	**DP/TXR #**	**Date**	**Title**
			Risk Assessment
B. O'Keefe	D405063	08/22/2013	Boscalid – Human Health Risk Assessment for a Section 3 Registration of New Uses on Globe Artichoke, Belgium Endive, Persimmon, Greenhouse Grown Tomato Transplants for the Home Consumer Market, and Residential Ornamentals, Landscape Gardens, Fruit Trees and Nut Trees; Plus Crop Group Expansions/Revisions for Bulb Vegetable Group 3-07, Fruiting Vegetable Group 8-10, Citrus Fruit Group 10-10, Pome Fruit Group 11-10, Berry Subgroups 13-07A, B, F, and G, Vegetable Root Subgroup 1B Except Sugar beet, and Oilseed Group 20.
			Residue Chemistry
S. Funk	D410742	04/30/2013	Boscalid: Petition for the Establishment of Permanent Tolerances and Registration for Use on Belgium Endive, Persimmon, and Globe Artichoke. Request for Crop Group Expansions/Revisions for Bulb Vegetable Group 3-07, Fruiting Vegetable 8-10, Citrus Fruit Group 10-10, Pome Fruit Group 11-10, Berry Subgroups 13-07A, B, F, and G, and Oilseed Group 20. Summary of Analytical Chemistry and Residue Data.
S. Funk	D398877	04/30/2013	Boscalid and Pyraclostrobin: Application by Bonide Products, Inc. to Register an End Use Product Containing Pyraclostrobin, Boscalid, and Lambda Cyhalothrin for Homeowner Use on Pome Fruit, Stone Fruit, and Tree Nuts.
S. Funk	D406471	04/30/2013	Pyraclostrobin and Boscalid: Request to Add Indoor Use on Greenhouse Tomato for Commercial Production and on Greenhouse/Lathhouse Transplants for Consumer Home Market. Pagent™ Fungicide Reg. No. 7969-251.
			Dietary Exposure Assessment
S. Funk	D410743	06/14/2013	Revised: Boscalid. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments to Support New Uses on Globe Artichoke, Belgium Endive, and Persimmon.
			Occupational and Residential Exposure Assessment
C. Walls	D455339	04/30/2013	Boscalid. Occupational and Residential Exposure Assessment for proposed new uses of boscalid on globe artichoke, Belgium endive, persimmon, greenhouse grown tomato transplants grown for home consumer market, and residential ornamentals, landscape gardens, fruit trees and nut trees.
			Incident Report
S. Recore	D418675	06/25/2014	Boscalid: Tier I Review of Human Incidents
			HASPOC Memoranda
K. Rury	TXR0056585	03/07/2013	Boscalid: Summary of Hazard and Science Policy Council (HASPOC) Meeting of February 14, 2013: Recommendations on the Waiver Request for the Subchronic Inhalation Study.
			CARC Report
J. Kidwell	TXR0051289	11/14/2002	BAS 510F: Report of Cancer Assessment Review Committee.

Attachments

1. Chemical Identity Table
2. Physicochemical Properties of Technical Grade Boscalid Table
3. Tolerance/MRL Summary Table
4. Endpoint Selection Tables
5. Toxicity Profile Tables

Attachment 1

Chemical Identity Table

Table 1. Nomenclature of Boscalid and its Hydroxy Metabolite.

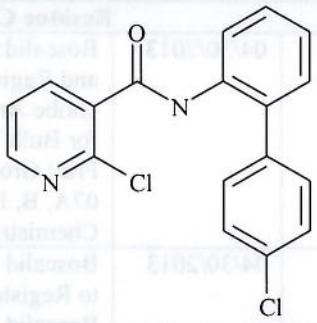
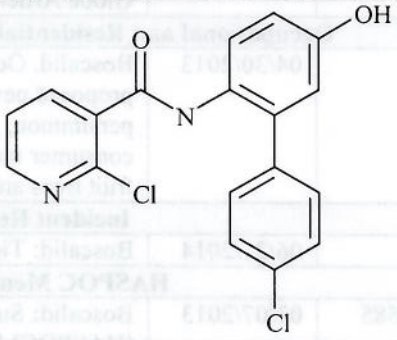
Compound	
Common name	Boscalid; Nicobifen
Company experimental name	BAS 510 F
IUPAC name	2-chloro-*N*-(4′-chlorobiphenyl-2-yl)nicotinamide
CAS name	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide
Molecular weight	343.2
CAS registry number	188425-85-6
End-use product (EPs)	25.2% WDG (Pristine® Fungicide; EPA Reg. No. 7969-199, also contains 12.8% pyraclostrobin) 70% WDG (Endura® Fungicide; EPA Reg. No. 7969-197)
Hydroxy-metabolite	
Common name	Boscalid hydroxy metabolite
Company experimental name	M510F01 (glucuronide conjugate – M510F02)
CAS name	2-chloro-N-(4'-chloro-5-hydroxy-biphenyl-2-yl)nicotinamide
Molecular weight	359.2

Table 2. Physicochemical Properties of Boscalid.		
Parameter	Value	References
Melting point/range	142.8-143.8 EC	MRIDs 45404802 and 45404804-45404809
pH	NA (does not dissociate in water)	
Relative Density (20°C)	1.381g/cm^3	
Water solubility (20°C)	4.64 mg/L at pH 6	
Solvent solubility (g/100 mL at 20°C)	acetone 16-20; ethyl acetate 6.7-8.0 methanol 4-5; 2-propanol <0.01 acetonitrile 4-5; dichloromethane 20-25 toluene 2-5; n-heptane <0.01 1-octanol <0.01; olive oil 2.9 N,N-DMF >25	
Vapor pressure	7 x 10^{-9} hPa	
Dissociation constant, pK_a	None (does not dissociate in water)	
Octanol/water partition coefficient, Log(K_{ow})	2.96	
UV/visible absorption spectrum	UV molecular extinction (e[lmol^{-1}cm^{-1}]): 3.15 x10^4 at 228 nm; 1.53 x10^3 at 290 nm	

Tolerance/MRL Tables

Boscalid (128008); (06/23/2014)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
40 CFR §180.589 (a)(1) And 40 CFR §180.589 (d) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′-chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide		-	Boscalid. The residue is fat soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*			
	US	Canada	Mexico[2]	Codex[3]
Alfalfa, forage	30.0	-		
Alfalfa, hay	65.0	-		
Almond, hulls	17	-		15
Animal feed, nongrass, group 18, forage, except alfalfa (inadvertent/indirect)	1.0	-		
Animal feed, nongrass, group 18, hay, except alfalfa (inadvertent/indirect)	2.0	-		
Animal feed, nongrass, group 18, seed (inadvertent/indirect)	0.05	-		
Apple, wet pomace	10	-		
Artichoke, globe	6.0	0.05 (Chinese, Jerusalem)		
Avocado	1.5	-		
Banana, import[4]	0.40	-		0.6
Beet, garden, roots (inadvertent/indirect)	0.1	1		
Beet, sugar, roots (inadvertent/indirect)	0.1	1		
Berry, low growing, subgroup 13-07G, except cranberry	4.5	-		3 (strawberry)
Brassica, head and stem, subgroup 5A	3.0	6		5
Brassica, leafy greens, subgroup 5B	18.0	50		
Bushberry subgroup 13-07B	13.0	11		10 (berries and small fruits)
Caneberry subgroup 13-07A	10.0	6		10 (berries and small fruits)
Canistel	1.5	-		
Canola, refined oil	5.0	5		
Citrus, dried pulp	4.5	-		6
Citrus, oil	85.0	-		50
Coffee, green bean, import[1]	0.05	-		0.05
Cotton, gin byproducts	55.0	-		
Cowpea, seed (inadvertent/indirect)	0.1	-		

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
40 CFR §180.589 (a)(1) And 40 CFR §180.589 (d) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′-chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide		-	Boscalid. The residue is fat soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*			
	US	Canada	Mexico[2]	Codex[3]
Cucumber	0.5	0.5		
Endive, Belgium	6.0	1		
Fruit, citrus, group 10-10	2.0	-		2
Fruit, pome, group 11-10	3.0	3		2 (apple)
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	5.0	3.5		5 (grapes)
Fruit, stone, group 12	3.5	1.7		3; (10, dried plums)
Grain, aspirated fractions	3.0	-		-
Grain, cereal, forage, fodder and straw, group 16, forage (inadvertent/indirect)	2.0	-		-
Grain, cereal, forage, fodder and straw, group 16, stover (inadvertent/indirect)	1.5	-		-
Grain, cereal, forage, fodder and straw, group 16, straw (inadvertent/indirect)	3.0	-		50 (oat and wheat and rye and barley straw and fodder, dry) 5 (straw of cereal grains except barley oat, wheat, and rye)
Grain, cereal, group 15 (inadvertent/indirect)	0.20	0.2		0.5 barley, oats, rye, wheat 0.1 (except barley, oats, rye, and wheat)
Grape, raisin	8.5	8.5		10
Grass, forage, fodder, and hay, group 17, forage (inadvertent/indirect)	2.0	-		
Grass, forage, fodder, and hay, group 17, hay (inadvertent/indirect)	8.0	-		
Grass, forage, fodder, and hay, group 17, seed screenings (inadvertent/indirect)	0.20	-		
Grass, forage, fodder, and hay, group 17, straw (inadvertent/indirect)	0.30	-		
Hop, dried cones	35	35		60
Leaf petioles subgroup 4B	45	45		30 (stalk and stem)
Leafy greens subgroup 4A, except head lettuce and leaf lettuce	60	60		40
Lettuce, head	6.5	6.5		
Lettuce, leaf	11.0	35		
Lupin, grain, grain (inadvertent residues)	0.1			
Mango	1.5	-		
Nut, tree, group 14	0.70	0.7		0.05 (*)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
40 CFR §180.589 (a)(1) And 40 CFR §180.589 (d) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4′-chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide		-	Boscalid. The residue is fat soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*			
	US	Canada	Mexico[2]	Codex[3]
Oilseed group 20	3.5	Cotton seed 0.05		1 (oilseeds)
Papaya	1.5	-		
Pea and bean, dried shelled, except soybean, subgroup 6C, except cowpea, field pea and grain lupin	2.5	2.5		3 (pulses)
Pea and bean, succulent shelled, subgroup 6B, except cowpea	0.6	0.6		3
Pea, field, seed (inadvertent residues)	0.1			
Peanut	0.05	0.05		
Peanut, meal	0.15	-		
Peanut, refined oil	0.15	0.15		
Peppermint, tops	30.0	30		
Persimmon	8.0	-		
Pistachio	0.70	0.7		1
Radish, roots (inadvertent residues)	0.1			
Rice, hulls (inadvertent residues)	0.50			
Sapodilla	1.5	-		
Sapote, black	1.5	-		
Sapote, mamey	1.5	-		
Soybean, hulls	0.2	-		
Soybean, seed	0.1	0.1		
Soybean, vegetable	2.0	1.6		
Spearmint, tops	30.0	30		
Star apple	1.5	-		
Turnip, greens	40.0	1		
Turnip, roots (inadvertent residues)	0.1			
Vegetable, bulb, group 3-07	5.0	3		5
Vegetable, cucurbit, group 9, except cucumber	1.6	1.5		3
Vegetable, foliage of legume, group 7, forage (inadvertent residues)	1.5			
Vegetable, foliage of legume, group 7, hay (inadvertent residues)	2.0			
Vegetable, foliage of legume, group 7, vines (inadvertent residues)	0.05			

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
40 CFR §180.589 (a)(1) And 40 CFR §180.589 (d) Boscalid, 3-pyridinecarboxamide, 2-chloro- *N* -(4'-chloro[1,1'-biphenyl]-2-yl)	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarbox-amide		-	Boscalid. The residue is fat soluble.
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*			
	US	Canada	Mexico[2]	Codex[3]
Vegetable, fruiting, group 8-10	3.0	1.4		3 (10, dried chili peppers)
Vegetable, leafy, except brassica, group 4, except celery, lettuce, and spinach (inadvertent residues)	1.0			
Vegetable, leaves of root and tuber, group 2 (inadvertent residues)	0.1			
Vegetable, legume, edible podded, subgroup 6A	1.6	1.6		
Vegetable, root, subgroup 1A, except sugar beet, garden beet, radish, and turnip	1.0	0.7 (carrot)		2
Vegetable, tuberous and corm, subgroup 1C	0.05	0.05		

[1] Includes all commodities with current US tolerances, as on 06/19/2014.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

[4]No US registrations as of September 16, 2009.

Boscalid (128008); (06/23/2014)

Summary of US and International Tolerances and Maximum Residue Limits			
Residue Definition:			
US	Canada	Mexico[2]	Codex[3]
40 CFR §180.589 (a)(2). sum of boscalid, 3-pyridinecarboxamide, 2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-, and metabolites 2-chloro-*N*-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide and glucuronic acid conjugate of 2-chloro-*N*-(4'-chloro-5-hydroxy-biphenyl-2-yl) nicotinamide, calculated as the stoichiometric equivalent of boscalid	2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide, including the metabolites 2-chloro-*N*-(4'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide and the glucuronic acid conjugate of 2-chloro-*N*-(4'-chloro-5-hydroxy-biphenyl-2-yl)nicotinamide	-	Boscalid. The residue is fat soluble.

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (ppm)*			
	US	Canada	Mexico[2]	Codex[3]
Cattle, fat	0.30	0.3		
Cattle, meat	0.10	0.1		0.7
Cattle, meat byproducts	0.35	0.35		0.2
Egg	0.02	0.02		0.02
Goat, fat	0.30	0.3		
Goat, meat	0.10	0.1		0.7
Goat, meat byproducts	0.35	0.35		0.2
Hog, fat	0.20	0.3		
Hog, meat	0.05	0.1		0.7
Hog, meat byproducts	0.10	0.35		0.2
Horse, fat	0.30	0.3		
Horse, meat	0.10	0.1		0.7
Horse, meat byproducts	0.35	0.35		0.2
Milk	0.10	0.1		0.1 (2 milk fats)
Poultry, fat	0.20	0.05		0.02
Poultry, meat	0.05	0.05		0.02
Poultry, meat byproducts	0.20	0.1		0.02
Sheep, fat	0.30	0.3		
Sheep, meat	0.10	0.1		
Sheep, meat byproducts	0.35	0.35		

[1] Includes all commodities with current US tolerances, as on 06/19/2014.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

Summary of Toxicity Endpoints and Points of Departure of Boscalid

Table 4.1. Summary of Toxicological Doses and Endpoints for Boscalid for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations, including Infants and Children and Females 13-49 years of age)	NA	NA	NA	An appropriate endpoint attributable to a single dose was not identified.
Chronic Dietary (All Populations)	NOAEL= 21.8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.218 mg/kg/day cPAD = 0.218 mg/kg/day	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Incidental Oral Short-Term (1-30 days) & Intermediate-Term (1-6 months)	NOAEL= 21.8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Dermal Short-Term (1-30 days) & Intermediate-Term (1-6 months)	NOAEL= 21.8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Inhalation Short-Term (1-30 days) & Intermediate-Term (1-6 months)	NOAEL= 21.8 mg/kg/day	UF_A = 10x UF_H = 10x UF_{DB} = 10x FQPA SF= 1x	Residential LOC for MOE = 1000	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Cancer (oral, dermal, inhalation)	Classification: "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"; quantification of human cancer risk is not recommended.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.2. Summary of Toxicological Doses and Endpoints for Boscalid for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days)	NOAEL= 21.8 mg/kg/day	UF_A = 10x UF_H =10x FQPA SF= 1x	Occupational LOC for MOE = 100	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Dermal Intermediate-Term (1-6 months)	NOAEL= 21.8 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Occupational LOC for MOE = 100	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Inhalation Short-Term (1-30 days)	NOAEL= 21.8 mg/kg/day	UF_A = 10x UF_H=10x UF_{DB} = 10x FQPA SF= 1x	Occupational LOC for MOE = 1000	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Inhalation Intermediate-term (1-6 months)	NOAEL= 21.8 mg/kg/day	UF_A = 10x UF_H =10x UF_{DB} = 10x FQPA SF = 1x	Occupational LOC for MOE = 1000	Co-critical chronic rat, carcinogenicity rat, and 1-year dog studies LOAEL = 57-58 mg/kg/day based on liver and thyroid effects
Cancer (oral, dermal, inhalation)	Classification: "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential"; quantification of human cancer risk is not recommended.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Toxicity Profile for Boscalid

Table 5.1. Acute Toxicity Profile – Boscalid (BAS 510 F) Technical.					
Test Material	**Guideline No.**	**Study Type**	**MRID**	**Results**	**Toxicity Category**
Technical	870.1100	Acute Oral - rat	45404814	LD_{50} > 5000 mg/kg	IV
Technical	870.1200	Acute Dermal - rat	45404815	LD_{50} > 2000 mg/kg	III
Technical	870.1300	Acute Inhalation	45404816	LC_{50} (M & F): > 6.7 mg/L	IV
Technical	870.2400	Primary Eye Irritation	45404817	Not irritating to the eye	IV
Technical	870.2500	Primary Dermal Irritation	45404818	Not irritating to the skin	IV
Technical	870.2600	Dermal Sensitization	45404819	Study unacceptable as challenge dose was inadequate	N/A

Table 5.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.3100 90-Day oral toxicity rodents (rat)	45404822 (2000) 0, 100, 500, 2000, 5000, 15,000 ppm 0, 7, 34, 137, 347, 1055 mg/kg bw/day Males 0, 8, 40, 159, 395, or 1225 mg/kg bw/day Females Acceptable/Guideline	**NOAEL**: 34/159 mg/kg/day (M/F) **LOAEL**: 137/395 mg/kg/day (M/F): M = increases in absolute and relative thyroid weights and increased incidence of thyroid hyperplasia as well as follicular epithelial hypertrophy; F = increases in absolute and relative thyroid weights.
870.3100 90-Day oral toxicity rodents (mouse)	45404821 (2000) 0, 150, 1000, 4000, 8000 ppm 0, 29, 197, 788, and 1518 mg/kg bw/day Males 0, 42, 277, 1184, and 2209 mg/kg bw/day Females Acceptable/Guideline	**NOAEL**: 197/2209 mg/kg/day (M/F) **LOAEL**: 788/2209 mg/kg/day (M/F): M = increased liver weights and increased incidence of marked fatty change in the liver; F = not attained
870.3150 90-Day oral toxicity in nonrodents (dog)	45404823 (2000) 0, 250, 2500, 25,000 ppm 0, 7.6, 78.1, 728.9 mg/kg/day Males 0, 8.1, 81.7, 824.8 mg/kg/day Females Acceptable/Guideline	**NOAEL**: 7.6/8.1 mg/kg/day (M/F) **LOAEL**: 78.1/81.7 mg/kg/day (M/F): M = increased alkaline phosphatase activity and hepatic weights; F = increased alkaline phosphatase activity and hepatic weights.

Table 5.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.3200 21/28-Day dermal toxicity (rat)	45404824 (2000) 0, 100, 250, or 1000 mg/kg bw/day Acceptable/Guideline	**NOAEL**: 1000 mg/kg/day (HDT) **LOAEL**: >1000 mg/kg/day
870.3700 Prenatal developmental in rodents (rat)	45404904 (2000) 0, 100, 300, 1000 mg/kg bw/day Acceptable/Guideline	**Maternal NOAEL**: 1000 mg/kg/day **Maternal LOAEL**: cannot be established **Developmental NOAEL**: 1000 mg/kg/day **Developmental LOAEL**: cannot be established
870.3700 Prenatal developmental in nonrodents (rabbit)	45404905 (2000) 0, 100, 300, 1000 mg/kg bw/day Acceptable/Guideline	**Maternal NOAEL**: 300 mg/kg/day **Maternal LOAEL**: 1000 mg/kg/day based on abortions or early delivery. **Developmental NOAEL**: 300 mg/kg/day **Developmental LOAEL**: 1000 mg/kg/day based on abortions or early delivery.
870.3800 Reproduction and fertility effects (rat)	45404906 (2001) 0, 100, 1000, 10,000 ppm F_0 parental animals 10.1, 101.2, 1034.5 mg/kg/day Males 10.7, 106.8, and 1062.0 mg/kg/day Females Acceptable/Guideline	**Parental systemic NOAEL**:112.6/1180.8 mg/kg/day (M/F) **Parental systemic LOAEL**:1165.0/>1180.8 mg/kg/day (M/F) decreased body weight and body weight gain (F_1) as well as hepatocyte degeneration F_0 and F_1) in males only. **Offspring systemic NOAEL**:11.2/115.8 mg/kg/day (M/F) **Offspring systemic LOAEL**:112.6/1180.8 mg/kg/day (M/F): decreased body weight for F_2 pups in males and females of both generations. **Reproductive NOAEL**:1165.0/1180.8 mg/kg/day (M/F) **Reproductive LOAEL**:>1165.0/1180.8 (M/F)
870.4100a Chronic toxicity rodents (rat)	45404827, 45723501 (2001) 0, 100, 500, 2500, 15,000 ppm 0, 4.4, 21.9, 110.0, 739.0 mg/kg bw/day for males and 0, 5.9, 30.0, 150.3, 1000.4 mg/kg bw/day for females Acceptable/Guideline	**NOAEL**: 21.9/30.0 mg/kg/day (M/F) **LOAEL**: 110.0/150.3 mg/kg/day (M/F): M = thyroid toxicity (weights and microscopic changes); F = thyroid toxicity (weights and microscopic changes). Thyroid follicular cell adenomas: M = 0/20, 0/20, 2/20,1/20; F = 0/20, 0/20, 1/20,0/20.
870.4100 Chronic toxicity (dog)	45404826 (2000) 0, 200, 800, 2000, 20,000 ppm 0, 5.5, 21.8, 57.4, 544.0 mg/kg bw/day Males 0, 5.8, 22.1, 58.3,592.9 mg/kg bw/day Females Acceptable/Guideline	**NOAEL**: 21.8/22.1mg/kg/day (M/F) **LOAEL**:57.4/58.3 mg/kg/day (M/F): M = elevated ALP activities and elevated hepatic weights; F = no effects

Table 5.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.4200 Carcinogenicity (rat)	45404828 (2001) 0, 100, 500, 2500, 15,000 ppm 0, 4.6, 23.0, 116.1, 768.8 mg/kg bw/day for males and 0, 6.0, 29.7, 155.6, 1024.4 mg/kg bw/day for females) Acceptable/Guideline	**NOAEL**: 23.0/29.7 mg/kg/day (M/F) **LOAEL**: 116.1/155.6 mg/kg/day (M/F): M = increased incidence of thyroid follicular cell hyperplasia and hypertrophy; F = decrease in body weight gain and increased incidence of thyroid follicular cell hyperplasia and hypertrophy. Thyroid follicular cell adenomas: M = 0/50, 0/50, 1/50, 4/50; F = 0/50, 1/50, 0/50, 3/50.
870.4200 Carcinogenicity (mouse)	45404901 (2001) 0, 80, 400, 2000, 8000 ppm 0, 13, 65, 331, 1345 mg/kg bw/day Males 0, 18, 90, 443, 1804 mg/kg bw/day Females) Acceptable/Guideline	**NOAEL**:65/443 mg/kg/day (M/F) **LOAEL**: 331/1804 mg/kg/day (M/F): M = decreases in body weight and body weight gains; F = decreases in body weight and body weight gains. No evidence of carcinogenicity.
870.5100 Gene Mutation bacterial reverse mutation assay	45404913 (1998) Initial concentrations: 22, 110, 550, 2750, 5500 µg/plate Repeat assay: 20, 100, 500, 2500, 5000 µg/plate Acceptable/Guideline	Negative without and with S-9 activation up to limit dose of 5000 µg/plate.
870.5300 *In vitro* mammalian cell forward gene mutation assay (CHO cells/HGPRT locus)	45404914 (2000) Initial concentrations: 15.625, 31.25, 62.5, 125, 250 or 500 µg/mL in the presence and absence of mammalian metabolic activation (S9-mix) Repeat concentrations: 10.24, 25.6, 64, 160, 400 1000 µg/mL with and without S9-mix with a repeat of the non-activated test at concentrations of 3.125, 6.25, 12.5, 25, 50, 100 µg/mL Acceptable/Guideline	Negative without and with S-9 activation up to the limit of solubility of 25 µg/mL.
870.5375 *In vitro* mammalian cytogenetics assay in Chinese hamster V79 cells	45404915 (1999) Initial exposure: 0, 20.0, 100.0 500.0 µg/mL with and without metabolic activation Second exposure: 0, 31.25, 62.5, 125.0 µg/mL in the absence of S9-mix Acceptable/Guideline	Negative without and with S-9 activation up to 3500 µg/mL with precipitation showing at concentrations of 100 µg/mL and higher.

Table 5.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.5395 Cytogenetics - mammalian erythrocyte micronucleus test in the mouse	45404916 (1999) 0, 500, 1000, 2000 mg/kg bw Acceptable/Guideline	Negative at doses up to 2000 mg/kg.
870.5500 *In vitro* unscheduled DNA synthesis (primary rat hepatocytes)	45404917 (2000) First: 0, 5, 10, 50, 100, 250, 500, 750, 1000 µg/mL Repeat due to excess cytotoxicity: 0, 0.5, 1.0, 5.0, 10.0, 50.0, 100.0, 250.0, 500.0 µg/mL A second experiment was conducted at 1.563, 3.125, 6.250, 12.500, 25.000, 50.000 µg/mL Acceptable/Guideline	Negative response up to 50 µg/mL. Cytotoxicity at 100-500 µg/mL.
870.6200a Acute neurotoxicity screening battery (rat)	45404820 (2000) 0, 500, 1000 or 2000 mg/kg bw Acceptable/Guideline	**NOAEL**:2000/1000 mg/kg/day (M/F) **LOAEL**: >2000/2000 mg/kg/day (M/F): F = piloerection
870.6200b Subchronic neurotoxicity screening battery (rat)	45404825 (2001) 0, 150, 1500, 15000 ppm 0, 10.5, 103.1 1050.0 mg/kg bw/day for males 0, 12.7, 124.5 or 1272.5 mg/kg bw/day for females Acceptable/Guideline	**NOAEL**:1050.0/1272.5 mg/kg/day (M/F) **LOAEL**: >1050.0/1272.5 mg/kg/day (M/F)
870.6300 Developmental neurotoxicity (rat)	45404907 (2001) 45800101 (2002) 45800102 (2002) 0, 100, 1000 10000 ppm 0, 14, 147 1442 mg/kg/day Acceptable/Guideline	**Maternal NOAEL:**1442 mg/kg/day **Maternal LOAEL:** >1442 mg/kg/day **Offspring NOAEL:** 14 mg/kg/day **Offspring LOAEL:** 147 mg/kg/day (decreased body weights on PND 4 and decreased body weight gain on PNDs 1-4)

Table 5.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
870.7485 Metabolism and pharmacokinetics (rat)	45404918 (2001) 45404919 (2000) 45692401 (2002) a single 50 or 500 mg/kg oral dose, or a 14-day repeated dose (500 mg/kg/day) Acceptable/Guideline	BAS 510 F was readily absorbed and excreted following single oral 50 mg/kg; at single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion mainly by feces (80-98%). Biliary excretion 40-50% of fecal activity at 50 mg/kg, 10% at 500 mg/kg. Urine, about 16% at 50 mg/kg, 3-5% at 500 mg/kg. Absorption about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns similar by gender or radiolabel position. Metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with glucuronic acid or sulfate, or by conjugation of the parent with glutathione with cleavage to sulfate metabolites.
870.7600 Dermal Penetration (rat)	45404920 (2001) 0.01, 0.10, 1.0 mg/cm^2 for 1, 4, 10, or 24 hours Acceptable/Guideline	Maximum % absorption: 0.01 mg/cm^2 = 10.93 (24 hour exposure, 24 hour sacrifice) 0.10 mg/cm^2 = 3.76 (24 hour exposure, 24 hour sacrifice) 1.00 mg/cm^2 = 1.48 (10 hour exposure, 72 hour sacrifice)
870.7800 Immunotoxicity	MRID 48203801 (2003) 0, 100, 1000, or 10000 ppm 0, 7.45, 73.1, or 736.2 m/k/d Acceptable / Guideline	NOAEL = 736.2 mg/kg/day LOAEL = not established
Non-guideline Hepatic enzyme induction (rat)	45404902 (1999) 0 or 15,000 ppm (equivalent to 0 or ~1500 mg/kg bw/day) for two weeks Acceptable/Non-guideline	1. hypertrophy of zone III hepatocytes 2. >20% increase in liver weight 3. increase in CYP450 activity 4. slight to extensive microscopic SER proliferation 5. not a peroxisome proliferator 6. enzymes in CYP450 subfamily not induced 7. no notable microscopic increase in size or number of peroxisomes CONCLUSION: inducer of total CYP450 activity
Non-guideline Hormone and enzyme induction (rat)	45404903 (2001) 0 or 15,000 ppm 0 or ~1000 mg/kg bw/day For four weeks Acceptable/Non-guideline	1. slight (statistically significant) decrease in circulating T_3 and T_4 only in males 2. increase in circulating TSH levels both sexes 3. increase in all 3 liver microsomal glucuronyltransferases CONCLUSION: disruption of thyroid homoeostasis by decreasing circulating T_3 and T_4 and increasing TSH; likely the result of hepatic microsomal glucuronyltransferase induction

Table 5.2 Repeated Dose Toxicity Profile of Boscalid (BAS 510 F) Technical.		
Guideline No. and Study Type	**MRID (date) Dose Levels Study Classification**	**Results**
Non-guideline Reversibility study (dietary): 4-week administration followed by 4 weeks recovery or 13 weeks recovery (rat)	45550601 (2001) 0, 100, 2500, 15000 ppm 0, 7.7, 190.3, 1137.4 mg/kg/day) Acceptable/Non-guideline	4 weeks dosing: at 2500 and 15000 ppm: increase in TSH (68% and 87%); increase in absolute and relative thyroid weights, hypertrophy of thyroid follicular epithelial cells and diffuse follicular hyperplasia, increase in absolute and relative liver weights and centrilobular hypertrophy as well as liver portal fatty changes. 4 weeks dosing + 4 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. 4 weeks dosing + 13 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. CONCLUSION: induction of liver microsomal enzyme system resulting in increased glucuronidation of thyroxine, resulting in an increase in TSH secretion as a compensatory response of the physiological negative feedback system; increased TSH resulted in increased thyroid weight.